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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,221	SANBERG ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87,89,90 and 93-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87,89,90 and 93-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The request for continued examination filed July 25, 2005 is acknowledged.

The amendment filed March 2, 2005 (hereinafter referred to as "the response") has been entered. Claims 87 and 89 have been amended. Claims 88, 91, and 112-123 have been cancelled.

Accordingly, Claims 87, 89, 90, and 93-98 remain pending.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2005 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87, 89, 90, and 96-98 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record, because the specification, while being enabling for

a method of producing an isolated, differentiated, mononuclear cell from human umbilical cord blood, comprising (a) obtaining a cord blood fraction comprising mononuclear cells from said umbilical cord blood, wherein the mononuclear cells comprise progenitor cells; and (b) growing said cord blood

fraction from step (a) in a culture medium containing an effective amount of **retinoic acid and NGF** for a period sufficient to differentiate the progenitor cell to a cell of interest,

does not reasonably provide enablement for the use of other differentiation agents or other combinations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For clarity, it is noted that culturing the cord blood mononuclear cells with retinoic acid and NGF does not fall within the scope of Claim 87. However, the claims could be readily amended to cover this scope.

The claims are directed to methods of producing neural cell compositions.

The specification fails to provide an enabling disclosure for the methods of making neural cell compositions because the specification teaches that the only use for the compositions produced is for therapeutic transplantation, but methods of transplantation of neural tissue or other cells into the CNS or PNS are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the compositions produced from the claimed method is for transplantation to produce a therapeutic effect but the specification does not adequately teach how to use the cell compositions produced by the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses the barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. Grados-Munro et al. (2003) further disclose that axon outgrowth inhibition is a major barrier to axon regeneration in the CNS. Various myelin-associated inhibitors have been identified and their *in vivo* inhibitory effects have been characterized. The authors contemplate that a combination of

approaches, including treatment to neutralize the inhibitory character of the CNS environment, may be required for CNS regenerative therapy (page 479). Other problems relating to appropriate environmental cues for axon guidance are also discussed. Filbin (2003) also discloses that inhibitors of axonal regeneration are present in the adult mammalian CNS and further discusses the inhibitory effect of glial scars which form after injury. Growth cone collapse is noted as the first event in inhibition of axonal growth and the response of neurons to inhibitors is discussed, including the current state of the art with regard to the intracellular inhibitory signalling pathway. Mehler et al. (1999) details the unpredictability and technical problems encountered in using progenitor cells for neural regeneration, particularly in the CNS. The authors state that "the reconstitution of more complex and widespread neural populations damaged by a variety of genetic or acquired neurological disorders such as stroke or traumatic injury will require access to a broader array of neural lineage species and a greater understanding of the developmental signals that sanction integration into the host environments. Many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitor species present in multiple mature CNS regions to realize their broad lineage potential" (page 781, column 2, paragraph 2). The instant specification does not offer specific guidance as to how the full scope of the compositions produced by the claimed method could be used therapeutically for the treatment of any disorder, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Tay Sach's disease, Rett Syndrome, lysosomal storage disease, ischemia, spinal cord damage, ataxia, schizophrenia, or autism, as contemplated in the specification. While the specification discloses the use of human cord blood fractions that have been used either directly upon thawing (cord blood mononuclear cells) or treated in culture for a week with various trophic factors (BDNF, NGF, EGF+bFGF) prior to transplantation into a rat stroke model (pages 58-65), the claims cover the preparation of a great variety of cell compositions, including terminally-differentiated cells, which the specification does not teach how to use. The human cord blood

fractions used directly upon thawing are not the cells produced by the claimed methods, but rather appear to be the starting material for use in the claimed method. **With regard to the cells that were cultured with various trophic factors, the specification does not disclose the phenotype of these cells and the claims require the production of cells that exhibit an increase in the expression of genes associated with neurogenesis.** The example at page 58 of the specification states that "[a]nimals which received the retinoic acid+NGF treated mononuclear cells were able to stay on a rotating axle longer and fell off fewer times in the 3 minute test period than did all other animals in the study." This statement is relied upon for the scope of enablement indicated hereinabove. However, nothing further is disclosed about the treatment of cord blood mononuclear cells with retinoic acid+NGF. The disclosure provides no specifics in terms of the length of time the cells were cultured in the presence of the factors, the amount of each factor, or other parameters of the culture conditions. Nothing is disclosed in terms of the "increase in expression of genes associated with neurogenesis and a decrease in the expression of genes associated with hematopoiesis" as recited in the claim. Thus, it is unclear that culture in the presence of retinoic acid+NGF meets the present claim limitations relating to the gene expression profile of the "cell of interest." Other than the stroke example presented at page 58, the specification provides general teachings only (see pages 1-8 of specification), but does not provide specific guidance for treating a pathological condition, using cell compositions over the full scope of the claims. The specification fails to provide specific guidance for using the great variety of cell compositions covered by the claims, to provide a therapeutic benefit for the treatment of a disease or disorder.

Given the limited applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of cell types and cell compositions that could be produced using the claimed methods, and the unpredictability for using the cell compositions produced to achieve a therapeutic effect upon transplantation as asserted in the specification, one of skill in the art would have been required to engage in undue experimentation to

practice the claimed methods to make cell compositions that meet the claim limitations and further to use the cell compositions produced by the claimed methods.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

At page 5 of the response, Applicants assert that they have amended Claim 87 to recite the various trophic factors listed on page 58 of the specification. Applicants further assert that these trophic factors were used to differentiate umbilical cord blood cells, which were then transplanted into a rat stroke model. However, for reasons of record and as reiterated hereinabove, the specification does not provide specific guidance with regard to the use of these various trophic factors, but instead simply states that cells "were treated in culture for a week with various trophic factors (BDNF, NGF, EGF+bFGF) prior to transplantation" (page 58, lines 7-8). There is no specific guidance with regard to how these "various trophic factors" were used in culturing the cells. Were all four factors used in combination? Was each factor used individually? Were EGF and bFGF used as one combination? Were other combinations used? As stated in the prior Office Action, "[w]ith regard to the cells that were cultured with various trophic factors, the specification does not disclose the phenotype of these cells and the claims require the production of cells that exhibit an increase in the expression of genes associated with neurogenesis." (page 4 of the Office Action of 9/23/04). Thus, reciting the "various trophic factors" mentioned in the example is not sufficient to overcome the enablement rejection. Absent a teaching of the phenotype of the cells produced upon treatment with the various trophic factors, the claim limitation reciting that phenotype is not met. Furthermore, no specific guidance is provided with regard to therapeutic results achieved with these "various trophic factors" upon transplantation into the rat stroke model. On the contrary, only the result obtained with cells cultured with retinoic acid and NGF is presented, although retinoic acid is not mentioned as one of the "various trophic factors" used in culturing the cord blood mononuclear cells.

Applicants have not offered any arguments explaining how the present claims overcome the enablement rejection of record.

Claims 93-95 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 93-95 are directed to the aforementioned method of producing an isolated, differentiated mononuclear cell from human umbilical cord blood, wherein the progenitor cells are isolated from the mononuclear cells prior to step (b).

The reasoning set forth above in the scope of enablement rejection applies equally to Claims 93-95. In addition, there is no scope of enablement for these claims for the following reasons. The claims require isolation of the progenitor cells from the mononuclear cells, but the specification fails to provide an enabling disclosure for separating the progenitor cells from the mononuclear cells.

The specification provides no guidance with regard to isolating the progenitor cell of interest from the cord blood mononuclear cells. The specification contemplates that the progenitor cell of interest may be a mesenchymal stem cell present in cord blood that has the capability to differentiate into neural cells and that it may therefore be a CD34-negative cell. However, the specification provides no fractionation methods beyond separating whole cord blood to obtain mononuclear cells and separating cord blood cells to obtain CD34-negative cells (page 27). The specification does not identify the cell type that is responsible for producing the neural cells appearing after differentiation. At pages 27-28 of the specification, the disclosure teaches how to obtain cord blood cells that are negative for CD34. However, this cell fraction is not further used in experiments to determine if it retains the progenitor cell that is responsible for producing the differentiated neural cells. The art demonstrates the difficulty of identifying

a desired progenitor or stem cell from a heterogeneous population of cells and the further difficulty of purifying or isolating that stem or progenitor cell from the heterogeneous cell population (Bonnet, 2002). For example, Bonnet discusses the difficulties encountered in identifying and separating distinct subpopulations of CD34+ cells to obtain hematopoietic stem cells with long-term repopulating capability. Although, hematopoietic stem cells have been studied for many years, the author discloses that "[t]he elucidation of the molecular phenotype of the HSC has just begun" (abstract).

Given the limited applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to separation methods that may be used to isolate the progenitor cells from the mononuclear cells, and the unpredictability for using the cell compositions produced to achieve a therapeutic effect upon transplantation as asserted in the specification, one of skill in the art would have been required to engage in undue experimentation to practice the claimed methods to make cell compositions that meet the claim limitations and further to use the cell compositions produced by the claimed methods.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87, 89, 90, and 93-98 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 89 and 90 are indefinite in their recitation of "wherein said differentiation agent comprises retinoic acid and NGF" because Claim 87, from which Claims 89 and 90 depend, does not cover mixtures of the various differentiation agents listed. Thus, Claims 89 and 90 fall outside the scope of Claim 87.

Claims 87, 89, 90, and 93-98 remain indefinite in their recitation of "increase" and "decrease" because it is unclear what would be considered the reference state for said "increase" or said "decrease". The claims now recite that the cell of interest should be compared to an "umbilical cord blood cell that has not been cultured in the presence of a differentiation agent" but the term "umbilical cord blood cell" covers a variety of different cell types, given that "umbilical cord blood" refers to a heterogeneous population of cells. Thus, it is unclear which cell type should be used as the reference cell. Is it the progenitor cell itself (i.e., the cell that gives rise to the cell of interest)? In the absence of recitation of some reference state or process for comparison said "increase" and said "decrease" remain indefinite.

At page 6 of the response, Applicants assert that they have amended Claim 87 to recite "an umbilical cord blood cell" and submit that the amendment overcomes the rejection. However, contrary to Applicants' assertion, this is the same claim language presented in Applicants' amendment filed June 28, 2004 (see Claim 87) which precipitated the rejection. Therefore, it is unclear how reverting back to the original language overcomes the rejection. Applicants have provided no arguments or reasons as to why they believe the amendment overcomes the rejection. Since "umbilical cord blood" refers to a heterogeneous population of cells it remains unclear which cell type should be used as the reference cell.

Conclusion

No claims are allowable.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER